REMARKS

Reconsideration and withdrawal of the rejections made against the pending claims is respectfully requested, in view of the above provided amendments, and the following remarks.

AMENDMENTS TO THE SPECIFICATION

Several paragraphs of the specification are amended, *supra*, in order to conform the spelling of " *Bacillus subtilis*" to standard U.S. spelling, and as requested by the Examiner, to correct several other informalities, and to conform the language to standard U.S. usage in several places. It is respectfully urged that no new matter is added by these conforming amendments.

AMENDMENTS TO THE CLAIMS

Claims 10-11, 13-14 and 22-27 are pending. Claims 1-9 and 15-21 are cancelled without prejudice to Applicants' right to pursue the subject matter of these claims in any further continuation, continuation-in-part or divisional patent application(s). Claims 10-11 and 13-14 are amended, as indicated *supra*, in order to more particularly set forth that which Applicants consider to be their invention. Claims 22-27 are new.

Amended claim 10 is directed to a modified cecropin A-magainin 2 peptide of SEQ ID NO: 1, of the (unmodified) CA-MA peptide, having the specified amino acid residue substitutions without the previous Markush-language. This amendment is supported by the specification generally, and in particular by the exemplified modified CA-MA peptide.

Amended claims 11, 13 and 14 are now directed to anti-bacterial and anti-fungal agents of the invention, comprising the same specific modifications of the CA-MA peptide of SEQ ID NO:1 as recited by claim 10. Anti-bacterial activity of the claimed peptide, e.g., against *Bacillus subtilis* and *Pseudomonas aeruginosa* was measured on LB agar plates, and the confirmation of anti-bacterial activity is shown in FIGs 1-5 (*see* Experimental Example 1).

Anti-fungal activity of the claimed peptide, e.g., against *Candida albicans* and *Trichosporon beigelii* was measured by the MTT assay method, and the confirmation of anti-fungal activity is shown by Table 2 (*see* Experimental Example 2).

New claims 22-24 are directed to anti-cancer agents of the invention. Anti-cancer activity claimed peptide, e.g., against human lung cancer cell line Calu-6, human stomach cell line SNU 601 and T-cell lymphoma cell line was measured by the MTT assay method and the confirmation of anti-cancer activity is illustrated by FIG. 6 (*see* Experimental Example 3). Further, Experimental Example 4 shows that the exemplified peptide was free from cytotoxic activity against red blood cells, thus confirming the specificity of the observed anti-cancer activity.

New claims 25-27 are directed with greater specificity to the modified peptide of SEQ ID NO: 2.

It is respectfully urged that the amendments to the claims are fully supported by the specification, and that no new matter is added.

PERFECTION OF FOREIGN PRIORITY

At item 4 of the Office Action, it appears that the Examiner has requested a translation of Korean Patent Application No. 2001-57837, in order to perfect the earliest priority date for this application. A copy of an English-language translation of Korean Patent Application No. 2001-57837 is enclosed herewith, together with the required cover sheet confirming that the translation is accurate.

Perfection of the September 19, 2001 priority date from Korean Patent Application No. 2001-57837 is respectfully requested.

OBJECTIONS TO THE SPECIFICATION

At item 6 of the Office Action, the Examiner has objected to several informalities in the text, and has requested correction. The Examiner's attention to this point is appreciated, and these and several other informalities have now been corrected. Thus, the above-provided amendments correct the spelling of *"Bacillus"* at page 12, line 7, and elsewhere. In addition, the spelling of *"Staphylococcus"* is corrected at page 22, line 25. The language of the specification is also conformed to usage within the specification and/or to standard U.S. usage in several other places, without the addition of new matter.

THE CLAIMS ARE DEFINITE
UNDER 35 USC 112, SECOND PARAGRAPH

At item 7 of the Office Action, the Examiner has rejected claims 10 and 12 under 35 U.S.C. 112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter. The Examiner has asked whether "Applicant intend that the modified CA-MA2 peptide can have at least any one of the possible thirteen (13) substitutions as set forth in lines 3-5 of claim 12 for example or does the peptide have to have all thirteen substitutions?"

Applicants respectfully disagree. It is respectfully urged that the Examiner has not stated any pertinent legal authority for this rejection. The mere recitation of a finite set of multiple alternatives does not render a claim invalid under 35 USC 112, second paragraph. However, in the interest of expeditious prosecution, amended claim 10, *et seq.* no longer have the Markush language. This amendment is made without prejudice to Applicants' right to prosecute the subject matter of these claims, with the substitutions stated in the alternative, in this application or in any further continuation, continuation-in-part or divisional patent application(s).

For all of these reasons, it is respectfully submitted that this ground of rejection has now been obviated.

THE CLAIMS ARE ENABLED
UNDER 35 USC 112, FIRST PARAGRAPH

At item 8 of the Office Action, the Examiner has rejected claims 9, 14 and 21 under 35 U.S.C. 112, first paragraph, as allegedly failing to comply with the enablement requirement merely for reciting that the subject is a "pharmaceutical composition."

Applicants respectfully disagree. Claim 9 is cancelled, thus obviating the rejection as to that claim. Claim 10 is not limited by any suggested use of the subject peptide. Claims 11 and 12 are now directed to the peptide as an anti-bacterial and/or anti-fungal agent, respectively. These are properties that are extensively supported and confirmed by the specification. The

Examiner has provided detailed reasons why he believes that a pharmaceutical composition would not be enabled by the instant specification, also relying upon guidance offered by the Manual of Patent Examining Procedure or MPEP at §2164.01(c). As stated by MPEP § 2164.01(c):

> If a statement of utility in the specification contains within it a connotation of how to use, and/or the art recognizes that standard modes of administration are known and contemplated, 35 U.S.C. 112 is satisfied. *In re Johnson*, 282 F.2d 370, 373, 127 USPQ 216, 219 (CCPA 1960); *In re Hitchings*, 342 F.2d 80, 87, 144 USPQ 637, 643 (CCPA 1965). See also *In re Brana,* 51 F.2d 1560, 1566, 34 USPQ2d 1437, 1441 (Fed. Cir. 1993).
>
> For example, it is not necessary to specify the dosage or method of use if it is known to one skilled in the art that such information could be obtained without undue experimentation. If one skilled in the art, based on knowledge of compounds having similar physiological or biological activity, would be able to discern an appropriate dosage or method of use without undue experimentation, this would be sufficient to satisfy 35 U.S.C. 112, first paragraph. The applicant need not demonstrate that the invention is completely safe.

As noted at the top of this Remarks Section, anti-bacterial activity of the inventive peptide was confirmed against *Bacillus subtilis* and *Pseudomonas aeruginosa*, e.g., as illustrated by FIGs 1 to 5 (referring to Experimental Example 1). Anti-fungal activity of the inventive peptide was confirmed against *Candida albicans* and *Trichosporon beigelii*, as illustrated by Table 2 (referring to Experimental Example 2). Anti-cancer activity of the inventive peptide was confirmed against human lung cancer cell line Calu-6, human stomach cell line SNU 601 and T-cell lymphoma cell line as illustrated by FIG. 6 (referring to Experimental Example 3). Further, the absence of anti-erythrocyte cytotoxic activity was confirmed by Experimental Example 4.

It is respectfully submitted that 35 USC § 112, first paragraph, as summarized by MPEP § 2164.01(c), requires no more than what is provided by the instant specification. It is submitted that the law does not require additional, particularized enablement, such as details of doses and routes of administration for these composition claims. For all of these reasons, it is respectfully urged that this rejection is obviated, and should not be re-imposed on any of the currently pending claims.

THE CLAIMED INVENTION IS NOVEL UNDER 35 USC 102(b)

At item 10 of the Office Action, the Examiner has rejected claims 9-12 under 35 U.S.C. 102(b) as allegedly anticipated by Shin et al 1998 (Biochemistry and Molecular Biology International, 44/6:1119-1126), Lee et al 1999 (J. Biochem. Mol. Biol. And Biophys., 2:243-248), Shin et al 2000 (J. Blochem. Molt Biol. And Biophys., 4:135-145), Oh et al 2000 (Biochemistry; 39:11855-11864), Kang et al *1998* (J. Peptide Research, 52:45-50), Shin et al 1999 (J. Peptide Research, 53:82-90) or Shin et al 1997 (J. Peptide Research, 50:279-285).

Applicants respectfully disagree. The Federal Circuit has explained the requirements of an anticipating reference, as follows:

> A patent is invalid for anticipation when the same device or method, having all of the elements and limitations contained in the claims, is described in a single prior art reference. ... [citations omitted] An anticipating reference must describe the patented subject matter with sufficient clarity and detail to establish that the subject matter existed and that its existence was recognized by persons of ordinary skill in the field of the invention... [citations omitted].

ATD v. Lydall, 159 F.3d 534, 48 USPQ2d 1321, at 1328 (Fed. Cir. 1998)

Thus, in order for a reference to anticipate a claimed invention, each and every element of the claim must be show by the reference, organized as required by the claim. The Examiner's attention is respectfully directed to claim 10, as amended.

> A modified cecropin A-magainin 2 peptide comprising a peptide of SEQ ID NO:2 wherein residues 9, 10 and 11 are each independently substituted by proline; residues 4, 8, 14 and 15 are each independently substituted by lysine; and residues 5, 6, 12, 13, 16 and 17 are each independently substituted by leucine.

It is respectfully submitted that none of the references cited by the Examiner describes or suggests the modified peptide of claim 10, *et seq,* that is required to have the recited amino acid substitutions at all of the 13 indicated peptide positions. The cited references are discussed, in brief, as follows.

Shin et al. 1998 (Biochemistry and Molecular Biology International, 44/6:1119-1126), describe CA-MA peptides with from 1-4 residues replaced, as indicated in that article on page

1122, Table 1, e.g., see peptide A13, where underlining indicates the substitutions.

Lee et al. 1999 (J. Biochem. Mol. Biol. And Biophys., 2:243-248), describe CA-MA peptides with from 1-3 residues replaced, as indicated in that article on page 245, Table 1, e.g., see Analog 7, where underlining indicates the substitutions.

Shin et al. 2000 (J. Blochem. Molt Biol. And Biophys., 4:135-145), describe CA-MA peptides with from 1-4 residues replaced, as indicated in that article on page 139, Table 1, e.g., see peptide P13, where underlining indicates the substitutions and Fig. 1, on the same page.

Oh et al. 2000 (Biochemistry; 39:11855-11864), describe CA-MA peptides with from 1-3 residues replaced, as indicated in that article on page 11856, Table 1, e.g., see peptide p2, under "remarks."

Kang et al. *1998* (J. Peptide Research, 52:45-50), describe CA-MA peptides with from 1-3 residues replaced, as indicated in that article on page 46, Table 1, e.g., see peptide A9, under "Remarks."

Shin ct al 1999 (J. Peptide Research, 53:82-90), describe CA-MA peptides with from 1-4 residues deleted or replaced, e.g., see page 82, discussing a Gly-Ile-Gly deletion, a Pro, Gly-Ile, Gly-Pro and Gly-Pro-Gly substitutions or insertions.

Shin et al. 1997 (J. Peptide Research, 50:279-285), describe CA-MA peptides with from 1-2 residues substituted, e.g., see pages 280-281, at Fig. 1 and Table 1, respectively.

For all of these reasons, it is respectfully urged that claim 10, and the remaining claims now pending, are fully novel over all of the cited references.

It may be helpful to explain that the present invention relates to cecropin A-magainin 2 peptides ("CA-MA") of SEQ ID NO: 1, that have been modified to provide, e.g., the peptide of SEQ ID NO:2. The inventive modified CA-MA peptides have unexpectedly been found to exhibit superior anti-bacterial, anti-fungal and anti-cancer activity, without the cytotoxicity that has previously been a problem with many previously reported CA-MA peptides. It is believed that these enhanced properties are provided by the increased + charge (provided by the inserted lysine residues), and by the hydrophobicity (provided by the inserted proline and leucine residues) resulting from the full thirteen substitutions into the CA-MA peptide of SEQ ID NO:1.

The Examiner has stated, in the paragraph bridging pages 7-8 of the Office Action, that:

> The prior art discloses the claimed invent/on. Since the Patent Office does not have the facilities for examining and comparing applicants' peptides with the peptides of the prior art reference, the burden is upon applicants to show a distinction between the material structural and functional characteristics of the claimed peptides and the peptides of the prior art. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

Applicants respectfully urge that claim 10, *et seq.*, as amended, obviates the rejections under 35 U.S.C. § 102. It is submitted that, by requiring substitutions at 13 different peptide positions, the pending claims can be readily compared to the cited references, as discussed *supra*, without requiring Applicants to provide more data. The Examiner is respectfully invited to show where any of the cited references, taken separately, or in any combination, teach or suggest the claimed CA-MA peptides with 13 different amino acid residue substitutions, that simultaneously increase both + charge and hydrophobicity by substituting the recited 3 kinds of amino acids (lysine, proline and leucine) for the specific thirteen amino acids of the unmodified CA-MA peptide.

Absent such a showing, it is respectfully urged that all pending claims are now in condition for allowance, and early action to that end is respectfully solicited.

At item 12 of the Office Action, the Examiner has also stated that, "The prior art made of record and not relied upon is considered pertinent to applicant's disclosure." If any of this additional art, of record, is considered by the Examiner to negate patentability of the currently pending claims, the Examiner is respectfully invited to identify any such reference or references, with specificity. Otherwise, Applicants assume that any references of record, not identified as negating the patentability of the pending claims, merely provide technical background.

CONCLUSION

This Response is believed to be timely submitted. However, in the event that it is determined that an Extension of Time is required, the Commissioner is authorized to treat this paper as the required petition for extension of time, and to charge any required fee to Deposit

Account No. 02-2275. If any other fee is determined to be required for entry of this paper, that fee may also be charged to the above-mentioned Deposit Account.

Respectfully submitted,

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By: _____

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